Exhibit IND20

UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA – WESTERN DIVISION

NEUROGRAFIX, a California corporation; WASHINGTON RESEARCH FOUNDATION, a not-for-profit Washington corporation,

Plaintiffs,

vs.

SIEMENS MEDICAL SOLUTIONS USA, INC., a Delaware corporation; and SIEMENS AKTIENGESELLSCHAFT, a German corporation,

Defendants.

SIEMENS MEDICAL SOLUTIONS USA, INC.,

Counterclaimant,

vs.

NEUROGRAFIX, and WASHINGTON RESEARCH FOUNDATION

Counterdefendants.

Case No. 10-CV-1990 MRP (RZx)

[Assigned to The Honorable Mariana R. Pfaelzer]

DECLARATION OF DR. R. NICK BRYAN, M.D., PhD, RESPONDING TO DR. FILLER'S SEPTEMBER 12, 2011 DECLARATION

I, R. Nick Bryan, declare and state as follows:

1. My credentials and experience, including my complete CV, were provided in my Opening Expert report served July 22, 2011.

2. I provide this declaration in response to the new opinions and analyses provided by Dr. Filler in his September 12, 2011 declaration ("Filler Opposition Declaration") and accompanying exhibits, which he submitted in support of Plaintiffs' Opposition to Siemens' Motion for Partial Summary Judgment of Indefiniteness of "Conspicuity."

3. As an initial matter, it appears that Dr. Filler used automated computer algorithms in a software program called Osirix to perform a form of "thresholding" and something called "region-growing" (i.e., a type of segmentation algorithm) in order to select the neural ROIs in his Exhibits 15, 16, and 20. Within imaging software, there are not only various computer functions to perform "thresholding" and "region-growing," but such software also requires inputting various parameters once the operator has chosen which function, amongst the many, they want to use, for example intensity range, edge contiguity, edge distance, and voxel distance. Depending on these choices, the resulting ROI will vary. In both the Filler Opposition Declaration and accompanying exhibits, however, Dr. Filler did not clearly identify which computer programs in Osirix he used, nor which parameters he entered into whatever program he used. To the best of my ability, in the limited time that was available since receiving Dr. Filler's declaration, and based on the incomplete description in Dr. Filler's declaration and exhibits, I have tried to determine how he did so.

A. <u>Non-Neural Region of Interest.</u>

4. According to the new Filler Opposition Declaration, the '360 patent teaches, for purposes of the non-neural region of interest ("ROI") used in the Plaintiffs' proposed "conspicuity" calculation (i.e., S_n/S_m), selecting a two-centimeter ROI surrounding the nerve/neural tissue. Filler Opposition Decl. ¶¶ 2-3, Ex. 15 & 16.

5. I disagree with Plaintiffs and Dr. Filler—the '360 patent does not teach, for purposes of the non-neural ROI, selecting a two-centimeter ROI surrounding the nerve to calculate conspicuity. And even if it did, using such an approach for selecting the non-neural ROI would still not provide an objective and reproducible way to perform the "conspicuity" measurement proposed by Plaintiffs (i.e., S_n/S_m).

6. The two-centimeter disclosure in the '360 patent ('360 patent 27:29-35) is not even describing how to draw an ROI for purposes of calculating conspicuity. Rather, as the paragraphs before and after the two-centimeter disclosure make clear, this portion of the '360 patent is explaining how to select an ROI for purposes of creating another kind of nerve image, which the patent calls an "axial projection" illustrated in Figure 22. *See* '360 patent 27:36-43.

7. Indeed, preceding the two-centimeter disclosure, the '360 patent explains that a series of images was produced, which "consisted of 41, three mm thick axial sections, a 256x256 matrix, zero mm skip, and two nex." *See* '360 patent 27:24-26. The '360 patent then explains that a two-centimeter ROI of the sciatic nerve is selected on each of the 41 images. Then, using those 41 ROIs, "[p]rojectional images" were purportedly obtained to create an "axial projection of the nerve" like the one shown in Figure 22 of the patent. *See* '360 patent 27:36-43. The two-centimeter disclosure in the '360 patent therefore is not explaining how to select an ROI for purposes of calculating conspicuity, nor would one of ordinary skill in the art think to use this disclosure for performing any sort of conspicuity measurement.

8. Moreover, even if the two-centimeter disclosure in the '360 patent was discussing how to measure conspicuity (which it is not), it is clear from the specification of the '360 patent that the two-centimeter disclosure is not discussing selecting an ROI for the non-neural tissue, as suggested by Dr. Filler. Rather, the two-centimeter disclosure relates to selecting an ROI for nerve tissue.[1] In particular, it is discussing placing a two-centimeter ROI on the sciatic nerve

[1] As I explained in ¶¶ 6-7, one of ordinary skill would not interpret the two-centimeter disclosure in the '360 patent as relating in any way to calculating conspicuity. But even if they did, the two-centimeter disclosure also does not sufficiently describe how to select the neural/nerve ROI. For example, this disclosure does not tell one of ordinary skill in the art where (i.e., position) on the

shown in Figures 20 and 21 of the '360 patent. *Id.* at 27:14-15, 31; Figs. 20 & 21. Several parts of the '360 patent support this conclusion, for example:

a. First, as I explained above, *see* ¶¶ 6-7, the two-centimeter disclosure is explaining how to make selections for purportedly creating an axial projection of the nerve. *See* '360 patent 27:36-47, Fig. 22. If one were using the two-centimeter ROI to select non-neural tissue, it would be impossible to create the axial projection of the nerve, as the '360 patent purports to show in Figure 22.

b. Second, the nerve that is being selected in Figures 20 and 21 of the '360 patent with the two-centimeter elliptical ROI is the sciatic nerve. *Id.* at 27:14-15, 31. The sciatic nerve is approximately two-centimeters in diameter. The two-centimeter elliptical ROI therefore corresponds to the approximate size and shape of the sciatic nerve in Figures 20 and 21. And since the images in Figures 20 and 21 of the '360 patent contain an injured sciatic nerve, the diameter of the sciatic nerve would be larger than a normal sciatic nerve, which further suggests that the two-centimeter ROI was intended to select the entire sciatic nerve tissue, and not any non-neural tissue surrounding the sciatic nerve. *See* '360 patent 27:12-24 ("nerve of a patient having a nerve graft"); 27:38-41 ("nerve graft").

c. Third, the two-centimeter disclosure in the '360 patent explains that the two-centimeter ROI "was selected to exclude blood vessels." *See* '360 patent 27:32-35. That is consistent with the two-centimeter ROI being a nerve ROI, and inconsistent with Dr. Filler's indication that it is a non-neural ROI. As explained in the '360 patent and by Plaintiffs' other expert, Dr. Brant-Zawadzki, one should exclude blood vessels when selecting the neural ROI. Indeed, Dr. Brant-Zawadzki emphasized in his Opening Report that one should use the technique of avoiding blood vessels when selecting the neural/nerve ROI. *See, e.g.*, Brant-Zawadzki

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nerve to place the ROI, which is important to the resulting signal intensity measurement as I explained in my Opening Report. *See* Bryan Opening Rep. ¶¶ 38-39, 46-49. Depending on where the operator places the ROI on the nerve, the signal intensity will vary greatly. *See, e.g.*, Bryan Opening Rep. ¶¶ 46-49, Ex. C. Fig. 8.

Opening Rep. ¶¶34-35. And later in the same section of the '360 patent, it further explains that "the results of this analysis can be used to distinguish bright regions associated with nerve from those associated with, for example, blood vessels or lymphatics." '360 patent 28:17-19. Yet, nothing in the '360 patent teaches excluding blood vessels from the non-neural tissue, which is not surprising since blood vessels are an example of non-neural tissue. In fact, claims 15 and 30 in the patent expressly require that the non-neural tissue "include[] blood vessels." '360 patent 40:2-3, 42:16-17.

9. Even if one used the method of selecting a two-centimeter ROI for the non-neural tissue that Dr. Filler proposes, there are many problems with doing so, for example:

a. For images containing an entire nerve tract (as opposed to just a cross section of the nerve like Figures 20 and 21 of the patent), selecting a two-centimeter elliptical ROI around the nerve ROI would necessarily include nerve tissue in the non-neural ROI. Indeed, in Exhibit 15 of Dr. Filler's Opposition Declaration, the two-centimeter non-neural ROI (in red) seems to include portions of nerve, here the brachial plexus. *See* Filler Opposition Decl. Ex. 15.

b. In addition, Dr. Filler appears to have modified the two-centimeter non-neural ROI in Exhibit 15 in order to attempt to reduce the amount of neural tissue contained in the non-neural ROI. *See* Filler Opposition Decl. Ex. 15. This is shown by the half-circle cut-outs visible on either side of the two-centimeter red ROI. However, the specification of the '360 patent, and in particular the two-centimeter disclosure relied upon by Plaintiffs and Dr. Filler, does not mention modifying the two-centimeter ROI in any way, let alone the way Dr. Filler did in Exhibit 15. Nor would one of ordinary skill in the art be able to reproducibly make these kinds of subjective modifications without detailed guidance. And despite Dr. Filler's modifications, it appears that neural tissue could still be contained in the non-neural two-centimeter ROI in his Exhibit 15. Thus, the process demonstrated in Exhibit 15 suffers from subjectivity and unreliability.

c. It appears that Dr. Filler manually modified to the two-centimeter ROI in Exhibit 15.[2] But as explained in my Opening Export Report, *see, e.g.*, ¶ 36, manually selecting an ROI is dependent upon the observer's subjective ability to visually distinguish the boundary between the neural and non-neural tissue. *See, e.g.*, Bryan Opening Rep. ¶ 36. There would be variation in the resulting signal intensity measurement of the non-neural ROI depending on how one modified the two-centimeter ROI.

d. In order to calculate conspicuity according to Plaintiffs' proposed method (S_n/S_m) and using the ROI selection process suggested in the Filler Opposition Declaration, an operator would have to select a first ROI just for the neural/nerve tissue, then draw (and modify, as shown by Dr. Filler's Exhibit 15) a two-centimeter ROI for the non-neural tissue surrounding the neural tissue. Then, the operator would be required to subtract or remove the signal intensity value of the neural ROI from the signal intensity of the non-neural ROI, so that only the signal intensity of the non-neural ROI was included in the two-centimeter ring of non-neural tissue surrounding the neural ROI. Only then could one compare the signal intensity of the neural ROI to that of the non-neural ROI. But there is no support in the '360 patent for this approach and it is not a method that one of ordinary skill would typically perform if asked to calculate the conspicuity of any structure, let alone a peripheral nerve.

e. Dr. Filler appears to have used some segmentation algorithm to try to identify the precise boundary of the nerve and then subtracted that signal from the two-centimeter ROI. As explained in my opening report, there are many available segmentation algorithms, and they will lead to different tissue boundary definitions, and I am not even aware of a segmentation algorithm that reliably works for peripheral nerves. Bryan Opening Rep. ¶ 40.

[2] As I noted before, Dr. Filler does not explain in the Filler Opposition Declaration or his Exhibits how he made the modifications to the red, non-neural ROI in Exhibit 15, but I have tried to the best of my ability to determine how he did so based on the limited information that Dr. Filler provided.

f. Moreover, even if one were to use the method proposed by Dr. Filler to select a two-centimeter non-neural ROI, there is nothing in the '360 patent disclosing, nor does Dr. Filler explain, how to make such a selection in conjunction with the neural ROI he selected in Exhibit 20 to the Filler Opposition Declaration. *See* Filler Opp. Decl. Ex. 20, Fig. C. The neural ROI created by Dr. Filler in Figure C of Exhibit 20 is larger than two-centimeters. *See id.* It is therefore impossible to select a two-centimeter non-neural ROI surrounding the neural ROI selected by Dr. Filler in this image.

B. Neural Region of Interest.

10. Dr. Filler now suggests that a way of selecting the neural ROI is by using a "thresholding" technique that, according to Dr. Filler, is demonstrated in his new exhibits, such as Exhibits 15, 16, and 20.[3] *See* Filler Opposition Decl. ¶ 7, Ex. 15, 16, and 20. I disagree, however, that the '360 patent discloses either the "thresholding" technique demonstrated by Dr. Filler or any "thresholding" technique that can be used to select the neural ROI.

a. In Dr. Filler's Opposition Declaration and corresponding Exhibits 15, 16, and 20, he appears to use a region-growing algorithm, which is very different than what is described in the patent and also different than what a person of ordinary skill in the art would understand "thresholding" to be. *See* Filler Opp. Decl. Ex. 15 ("segmentation preview"); Ex. 16 ("growing region"); Ex. 20 ("2D growing region"). A region-growing algorithm is a type of segmentation algorithm that uses an initial "seed" pixel, and then determines whether the neighboring pixels should be part of the region based on their similarity to the "seed" pixel. The disclosure in the '360 patent of a "thresholding" processes (*see* '360 patent 28:2-7), however, does not mention nor suggest using a region-growing algorithm. An example of a "thresholding"

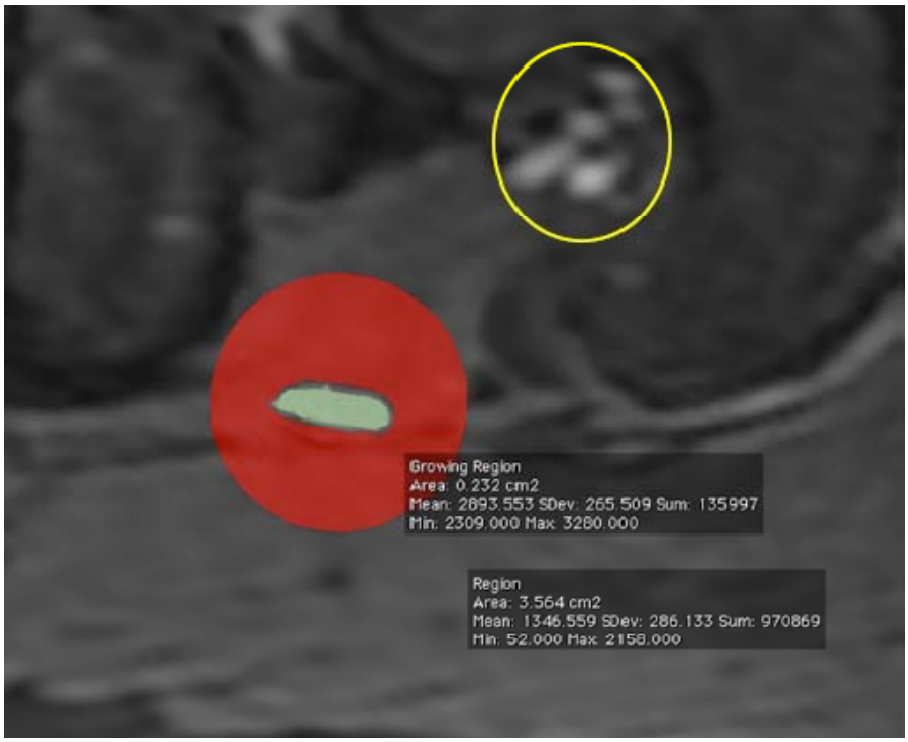
[3] While neither the Filler Opposition Declaration nor the accompanying Exhibits provide any detail about how Dr. Filler performed his measurements, it appears that Dr. Filler used different automated methods in the Osirix program for creating the neural ROIs in Exhibits 15, 16, and 20. ("segmentation preview" used for neural ROI), *with* Ex. 16 ("growing region" used for neural ROI). It is not clear that other imaging software, such as ImageJ, even has these same functions or capabilities.

process was shown in Exhibit 2 to my Rebuttal Export Report. Because of the difference between thresholding and region growing, one of ordinary skill in the art would not know to use a region-growing algorithm based on the disclosure in the '360 patent.

b. While the '360 patent leaves open the possibility of selecting an ROI "automatically," it does not disclose which of the various "automatic" techniques to use. Similarly, while Dr. Filler apparently used an automated function in Osirix to select the neural ROI, he did not explain why he chose the particular automatic function he used, amongst various ones available, nor did he explain the specific parameters he used as inputs to the particular function. But as explained in my Opening Expert Report, each of the various "automated" ways will produce different ROIs, and so will changing the parameters inputted into a particular function. *See* Bryan Opening Rep. ¶ 40. For example, an operator can specify the intensity range, edge contiguity, edge distance, and voxel distance**.** Accordingly, because different ROIs will be produced based on which automated function is used and on which parameters are inputted, the mean signal intensity of these ROIs will also change.

c. Even if one were to use what is typically known in the art as "thresholding," it would not help in determining which pixels or areas are neural tissue, much less precisely define the neural ROI, as explained in my Rebuttal Expert Report. *See* Bryan Rebuttal Rep. ¶¶ 20-25, Ex. 2. This is because, even if one of ordinary skill in the art were to use the brightest 50% of the pixel intensities as a threshold for determining which pixels are, or might be, neural tissue and which are not, such an approach would not isolate neural tissue in the images Plaintiffs contend were created by the patented method. In those images, non-neural tissue is often brighter than the neural tissue. Considering that the '360 patent repeatedly states that the nerves are brighter than any other structure in the image, it would be logical to think that these bright areas represent nerve. *See, e.g.*, '360 patent 23:58-59 ("nerves are brighter than any other structure in the image"); 6:43-44 ("results in the nerve signal being more intense than any other tissue"). But they are not. *See* Bryan Reb. Rep. Ex. 2. In fact, in Dr. Filler's new Exhibit 16, I have highlighted below (annotated with a yellow circle) a section of the image that is just as

bright as the nerve tissue and appears to have a fascicle pattern (which Dr. Filler and the '360 patent contend is indicative of a nerve). Yet, this structure is almost certainly not a nerve.



d. According to Plaintiffs and Dr. Filler, the "thresholding" disclosure in the '360 patent is used to select the final neural ROI. Based on my review, however, the '360 patent does not suggest the "thresholding" process is used to select the final ROI for the nerve. Rather, at most, the '360 patent suggests "thresholding" can be used to help "identify relatively bright regions of the image ***potentially*** representative of nerve." '360 patent 28:2-4. Thereafter, one would still have to select an ROI within the region that is potentially a nerve, but the '360 patent does not disclose how to make such selection.

11. Finally, regardless of whether one did use the method of selecting the neural and non-neural ROIs that Plaintiffs and Dr. Filler now propose, there would still be variation in the resulting measurement of "conspicuity," as shown in my Opening Expert Report, *see, e.g.*, Ex. C, Figs. 5 & 6.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on: September 22, 2011

Dr. R. Nick Bryan, M.D., PhD